REMARKS

I. Claim Amendments

The Claims have been amended according to the election in response to the restriction requirement, communicated on October 5, 2010.

Moreover, SEQ ID NOs: 248 and 249 have been included in claims 7, 9, 14, 19, 23, 29, 30, 31 and 32. These sequences represent treated unmethylated sense and antisense strand, both of which are variants of SEQ ID NO: 36 (Histone H4) and disclosed e.g. in Table 4 and 26 (pages 73 and 140-143 of the description).

Following entry of this amendment, claims 1-10, 14-18 and 27-37 are pending.

Accordingly, no new subject matter has been added.

II. Claim Rejections under 35 USC § 112

Claims 1-10, 14-18 and 28-32 stand rejected under 35 USC § 112, for failing to comply with the written description requirement. They allegedly include subject matter which was not described in the specification in such a way as to convey the one skilled in the art that the inventors at the date of filling, had possession of the claimed invention. Applicants respectfully traverse the rejection and note that the rejection is moot with respect to cancelled claim 28.

According to the current office action, the claim scope broadly encompasses any nucleotide capable of binding to SEQ ID NO: 36, 130, 131 and 1023 and variants of primer/probe sequences under stringent conditions. As a consequence, the claims allegedly are open to any nucleic acid sequence, with any degree of complementarity to SEQ ID NO: 36, 130, 131 and 1023. Especially, the claims would fail to include limitations regarding the minimum number of complementary nucleic acids which meet the limitation of "complementary to, or hybridizes under modestly stringent conditions". Applicants respectfully traverse the rejection, at least for the reasons below.

First, the sequence according to SEQ ID NO: 1023 has been withdrawn therefore the respective rejection should therefore be moot.

Second, responsive to the above-mentioned rejections, the term "essentially" has been deleted in claim 1 and 3, limiting the claims to "target nucleic acids comprising all or part of the sequence of the gene Histone H4". Moreover, claim 3 has been deleted and amended claims 1 and 4 do not recite "any sequences" that hybridize to one of the sequences of Histone H4 or SEQ ID NO: 36, 130, 131 under modestly stringent conditions, and therefore do not encompass any nucleotide capable of binding to one of these sequences. Rather, the claims only refer to "target sequences, comprising all or parts of the gene Histone H4". Therefore, the rejection regarding these claims should be moot. The same holds true for the bisulfite-treated, but unmethylated fragments of the Histone H4 gene, identified by SEQ ID NOs: 248 and 249 and included by the currently amended set of claims.

Third, regarding the sequences according to "all or part of Histone H4 and SEQ ID NO: 36, 130, 131", Applicants respectfully submit that in order to satisfy the requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750F.2d 1569, 224 USPQ 409 (Fed. Cir., 1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to each one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 471 F.2d 1237,176 USPQ 331, at 333 (CCPA 1973), emphasis in original. A patentee is not only allowed to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. In re Anderson, at 1241 (citing Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 [1935]). Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it. In re Grimme, Keil and Schmitz, 124 USPQ, 499, 502 (CCPA 1960). There is, therefore, no requirement for disclosure of every species within a genus. Applicant is entitled to

claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which Applicant has disclosed.

Further, Applicants respectfully submit that narrowing the scope of the current claims to the exact sequences as disclosed would result in an unfair limitation of the scope of protection for the Applicant. The resulting patent would be easily circumventable by competitors in the field, as the exchange of a single nucleotide would render the resulting sequence new with respect to the instant application. However, the instantly claimed invention is not directed to distinct nucleic acid sequences but rather to a method for the detection (and/or differentiation) of prostate cancer by using target sequences, comprising all or part of the claimed sequences.

Applicants respectfully request withdrawal of the rejection.

III. Claim Rejections under 35 USC § 102

Claims 1-4, 14-18 and 27-37 stand rejected under 35 USC 102(a) or (e) as being anticipated by Distler et al. (WO02/103042). Applicants respectfully traverse the rejection and note that it is moot with respect to the cancelled claims.

With regard to claim 1, the office action cites Distler for teaching a method for the detection of and/or differentiation between prostate cell proliferative disorders, comprising:

a) contacting genomic DNA with at least one reagent that distinguishes between methylated and non-methylated CpG dinucleotides within one or a combination of target nucleic acids,
b) each of said target nucleic acids comprising essentially all or part of a gene or a genomic sequence taken from the group consisting of SEQ ID NO: 1023 and Histone H4, wherein
c) said contiguous nucleotides comprise at least one CpG dinucleotide sequence, and whereby
d) the detection and/differentiation between prostate cell proliferative disorders is, at least in part, afforded.

In the Abstract and in Example 2, Distler allegedly discloses the differentiation of prostate cancer, based on the analysis of the methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in table 1.

Applicants respectfully traverse the subject rejection. In contrast to the Examiner's view, neither in the abstract, nor in Example 2, Distler et al. disclose target sequences comprising all or parts of the gene Histone H4. The abstract does not provide any information on particular genes or genomic sequences, the methylation status of which can be used to differentiate between prostate cell proliferative disorders. In table 1 to which Example 2 refers, Distler et al. names a list of 56 genes that are subjected to methylation analysis in order to distinguish between benign prostate hyperplasia and prostate carcinoma. However, Histone H4 is not included by this list, nor is it mentioned in Example 2. Rather, Example 2 names the TGF-alpha and POMC genes as including the most informative CpG positions (p. 15, 2nd par.).

Claim 1 has been amended, such that it no further refers to nucleic acids which comprise "***essentially*** all or part" of the target nucleic acid sequences. Moreover, all target genes and sequences have been withdrawn, except for the gene Histone H4. Accordingly, the scope of amended claim 1 only encompasses nucleic acids which do not include at least a part of the sequence of Histone H4.

However, Distler et al. is completely silent about Histone H4 and parts of its sequence. Consequently, claim 1 is not anticipated by the teachings of Distler et al.

Claim 4 depends on novel claim 1 and introduces the additional limitation of detection/distinction of prostate carcinoma/neoplasm. The claim is therefore not anticipated by Distler et al.

On page 10 of the OA, the Examiner states that Distler et al. anticipates claim 14, as any sequence taught by Distler would fall under the scope of SEQ ID NO: 130 and 131 and "complements thereof", as included by claim 14. Applicants respectfully traverse this rejection. Distler et al. does not teach the claimed sequences SEQ ID NO: 130 and 131. However, the Examiner seemingly construes the wording "and complements thereof" as "and any parts

thereof", whereby any nucleic acid sequence may fall under the scope of the claim. In contrast thereto, complementary sequences to SEQ ID NO: 130 and 131 are no arbitrary nucleotide sequences. Rather the nucleotide identity at every given position of a complementary strand is determined by the sequences of SEQ ID NO: 130 and 131. Also, the limitation of hybridizing under moderately stringent conditions does not render the claim open to any nucleotide sequence. It is well known to the person skilled in the art that nucleic acids which hybridize to each other under moderately stringent conditions still have to be complementary to each other, although mispairings may be allowable to a certain degree. Accordingly, current claim 14 is open to sequences that are complementary to SEQ ID NO: 130, 131, 248 and 249, whereas the complementarity may be below 100%. However, the sequences as disclosed by Distler et al. are completely unrelated to those encompassed by claim 14. Therefore, the claim is not anticipated by Distler et al.

Claims 15-18 and 27-37 all ultimately depend on claim 14 which is not anticipated by Distler et al. Accordingly, these claims are also not anticipated by Distler et al.

In view of the above-mentioned arguments, none of claims 1, 4, 14-18 and 27-37 is anticipated by Distler et al.; the rejections under 35 USC 102(a) or (e) should therefore be moot. Accordingly, Applicants respectfully request withdrawal of the claims.

IV. Claim Rejections under 35 USC § 103

Claims 5-10 and 29-37 are rejected under 35 USC § 103(a) as being unpatentable over Distler et al. (WO92/103042) in view of Wang et al. (US Patent H002220) and Buck et al. (Biotechniques 1999, 27, p. 528-536). On page 26, the office action states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Distler to include additional targets for the methylation analysis and to include primers for amplification as taught by Wang. Applicants respectfully traverse the rejection.

Applicants traverse this basis of rejection and submit that the Examiner has not established a *prima facie* case of obviousness. The Examiner must at a minimum demonstrate

that the cited references teach or suggest all the claim features, and even assuming, *arguendo,* that the references teach each claim feature, the Examiner must provide an explicit, apparent reason to practice these features in the fashion claimed by the Applicants with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). However, the Examiner has not shown that the cited references teach or suggest performing a methylation analysis of Histone H4 in order to detect or differentiate prostate cancer and the Examiner has not established the requisite motivation to practice the presently claimed subject matter with a reasonable expectation of success.

SEQ ID NO: 865335 may share some sequence homology with SEQ ID NO: 1023. However SEQ ID NO: 1023 has been withdrawn; therefore the rejection should be moot. Moreover, the gene sequences of Histone H4 and SEQ ID NO: 36 are not disclosed by Wang et al.; therefore these sequences cannot be rendered obvious by the cited references.

Only SEQ ID NO: 130 and 131 share some homology with SEQ ID NO: 793719 as cited for Wang et al., so if at all, these two sequences could be obvious in view of the cited prior art.

However, the person skilled in the art would not have been motivated by the prior art disclosures to combine the teachings of Distler with the sequences disclosed by Wang. Distler teaches nucleic acids and PNA oligomers for the diagnosis of prostate cancer by analysis of their cytosine methylation status, whereas Wang provides "a very large number of SNP probes (i.e. a total of 1,226,818) throughout the entire human genome". Importantly, none of these SNP probes is described as being suitable for (i) the analysis of cytosine methylation and (ii) the detection and differentiation of prostate cancer.

This is not surprising, since methods for mutational analysis are not *per se* suitable for the analysis of bisulfite-converted DNA without preceding, extensive experimental work. As was evident to the person skilled in the art at the time of filing, DNA after bisulfite conversion shows at least the following structural differences regarding to genomic, bacterial or viral DNA, which is the target for SNP analysis:

Differences between bisulfite-treated and genomic DNA

1. After bisulfite treatment, DNA largely consists of three instead of four different nucleotides, since all unmethylated cytosines are converted to uracil, or eventually (after amplification) to thymidine. Only methylated cytosines in the CpG sequence context remain cytosines. This results in a reduced sequence complexity, whereby the likelihood of sequence recurrences is much higher as compared to DNA not treated with bisulfite. The design of primers and probes which accurately detect specific sequences is therefore much more challenging as it is for regular "four-base DNA".

2. Bisulfite treatment generally results in highly degraded DNA, *i.e.* bisulfite-treatment provides for DNA being present only in short fragments. The degradation of DNA during bisulfite conversion is caused by high temperatures maintained over a long period of time (55 °C for 16 h), and acidic reaction conditions, resulting in so-called "abasic sites" within the nucleic acid strand, which are positions in the sequence without a base, and at which the DNA is cleaved during the subsequent desulfonation step. After bisulfite conversion, DNA is therefore present as a complex mixture of fragments with different lengths (see, e.g. Grunau et al. 2001, Nucleic Acid Research, 2001, 29(13):E65-5; copy enclosed).

3. After bisulfite conversion the DNA fragments also form a complex mixture regarding the conversion status of individual DNA molecules, i.e. at a distinct cytosine position, some fragments contain the converted cytosine (i.e. uracil), while others still contain the original cytosine at this position (see, e.g. Grunau et al. 2001, Nucleic Acid Research, 2001, 29(13):E65-5).

Moreover, SEQ ID NO: 130 and 131 represent oligonucleotides that are used as primers or blockers for methylation specific PCR methods (see e.g. page 34, lines 22 to 34: *"Particularly preferred are MethyLight, MSP and the use of blocking oligonucleotides as will be described*

herein. [...] It is further preferred that any oligonucleotides used in such analysis (including primers, blocking oligonucleotides and detection probes) should be reverse complementary, [...] to the base sequences of one or more of SEQ ID NO: [...] 130, 131, [...] and sequences complementary thereto."). According to their function, SEQ ID NO: 130 and 131 are bisulfite-treated sequences (see e.g. table 4: SEQ ID NO: 130 = Treated Methylated sense strand; SEQ ID NO: 131: Treated Methylated antisense strand). These sequences result from the conversion of unmethylated cytosines to uracil (and thymine after amplification), whereas SEQ ID NO: 793719 disclosed in Wang et al. represents human genomic, i.e. unmethylated DNA.

However, a person of skill in the art, knowing the above-mentioned differences between methylated and unmethylated DNA, would not have searched a database of 1,226,818 individual sequences of human genomic DNA in order to identify primer oligonucleotides, suitable for methylation-specific PCR reactions.

The examiner further cites Buck et al. (Biotechniques 1999, 27, p. 528-536) for teaching the functional equivalence of structurally homologous primer oligonucleotides (page 27). However, it is not doubted that a primer of a given structure (i.e. nucleotide sequence) exerts identical hybridization behaviour as a primer derived from a different biochemical source but with the same nucleotide sequence. But because of the above-mentioned arguments, the skilled person would not have had a reason to search the SNP database disclosed by Wang et al. for methylation-specific oligonucleotides that are suitable to amplify fragments of the Histone H4 gene. Again, mutational analysis of genomic DNA via SNPs is a different field as methylation analysis and the person skilled in the art was aware of the structural differences between genomic and bisulfite-treated DNA. By combining the prior art references, said skilled person would therefore not have arrived by the instant invention. In order to identify additional nucleic acid sequences for the Distler method, (i.e. suitable for determination of prostate cancer and benign hyperplasia), said skilled person would have searched among bisulfite-treated sequences and not within the extensive databases of un-treated SNP sequences as disclosed by Wang.

Accordingly, it was not obvious for the skilled person to combine an SNP database with a method for methylation analysis. Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

Please charge Deposit Account No. 07-1896 in the amount of $65.00 to cover a One Month Petition for Extension of Time fee. No additional fee is believed to be due in connection with this submission. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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